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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/984,900	12/04/97	D'APICE	A [illegible]

EXAMINER	
CHEN, S.	
ART UNIT	PAPER NUMBER
1633	11

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DATE MAILED: 03/30/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/984,900	Anthony J.F. D'Apice et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3 and 46-67* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3 and 46-67* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This is application is a continuation of Application No. 08/378,617 which was filed on 1-26-95, issued as US Patent No. 5,849,991, which is a continuation-in-part of Application No. 08/188,607 filed on 1-27-94, abandoned on 7-1-95. Applicants claimed priority of the filing date 1-26-95 of Application No. 08/378,617.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

> It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

To claim the present application as a continuation-in-part of prior application, it is required to list parent application in "duty to disclose" section.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

3. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Sandrin et al., 1995 (X).

Claim 1 is directed to nucleic acid molecule comprising SEQ ID No.7, SEQ ID No.7 within the scope of the degeneracy of the genetic code, and sequences hybridize to SEQ ID No.7 under standard high stringency condition. Sandrin et al. publishes a α-1,3 galactosyltransferase cDNA sequence, GenBank Accession No. L36535, which is 84.6% homologous (from base 108-1334) to SEQ ID No.7 of the present application. Thus, claim 1 is clearly anticipated by Sandrin et al..

4. Claims 3 is rejected under 35 U.S.C. 102(a) as being anticipated by Gustafsson et al., 1994 (W).

Claims 3 is directed to a porcine α-1,3 galactosyltransferase encoded by said nucleic acid molecule set forth above. Gustafsson et al. indicates the isolation of a pig α-1,3 galactosyltransferase cDNA sequence and its putative encoded protein contains 371 amino acids

that can be divided into four distinct regions reminiscent of other glycosyltransferases. Thus, claim 3 is clearly anticipated by Gustafsson et al..

5. Claims 1-3 and 67 are rejected under 35 U.S.C. 102(e) as being anticipated by Sandrin and McKenzie, 1998 (A).

Claims 1-3 and 67 are drawn to nucleic acid molecule comprising SEQ ID No.7, SEQ ID No.7 within the scope of the degeneracy of the genetic code, sequences hybridize to SEQ ID No.7 under standard high stringency condition, a protein encoded by said nucleic acid molecule, host cells transformed with said nucleic acid sequence, and a porcine containing at least one inactivated α-1,3 galactosyltransferase gene. Sandrin and McKenzie show the cDNA sequence and predicted amino acid sequence of a porcine Galα(1,3) galactosyl transferase gene (SEQ ID No.2), and a porcine cell comprising an inactivated porcine α(1,3) galactosyl transferase gene with a deletion, an insertion, a substitution, or an addition so that immune reaction of the cell with human antibodies reactive with Galα(1,3) Gal epitopes is avoided. Thus, claims 1-3 and 67 are clearly anticipated by Sandrin and McKenzie.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are vague and indefinite as the phrase "standard high stringency conditions" is indefinite. It is not clear what constitutes "standard high stringency conditions". The specification only gives an example of "high stringency conditions", but fails to define "standard high stringency conditions".

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 61-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp. 32639-32645 (also available at www.uspto.gov).

Claims 61-66 are drawn to a transgenic pig homozygous for an inactivated α-1,3 galactosyltransferase gene, and the cells and cell lines derived from said transgenic pig. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete

structure. (It is not realistic to expect that the "complete structure" of a pig, or even a cell, could be described. Therefore, the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype been described.) In this case, α-1,3 galactosyltransferase homologous knockout mice were produced Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of expressing a transgene can not be predicted. The phenotype is unpredictable. The specification does not disclose any other type of transgenic animal homologous for an inactivated α-1,3 galactosyltransferase gene. Therefore, the written description is not sufficient to inform a skilled artisan that applicants were in possession of the transgenic pig, the cells and cell lines derived from said transgenic pig recited in the claims at the time of filing. Thus it is concluded that the written description requirement is not satisfied for the claimed species.

9. Claims 52-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 52-66 are drawn to a method of generating a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase gene by introducing a DNA construct comprising said

inactivated gene into porcine ES, PGC, or egg; a method for generating a transgenic pig homozygous for an inactivated α-1,3 galactosyltransferase gene by manipulating a porcine cell comprising at least one said inactivated gene into embryo, or by injecting porcine ES cell containing at least one said inactivated gene into a porcine blastocyst or porcine morula, or co-culturing said ES cell with a zona pellucida-disrupted porcine morula, or fusing said porcine cell with an enucleated porcine oocyte, the transgenic pig produced by said method, and the cells and cell line derived from said transgenic pig. The specification discloses the purification of human anti-gal antibody, inhibition of human serum-induced lysis of porcine cells by sugars, e.g. melibiose, galactose, or by depleting anti-gal antibody in the serum, characterization of porcine α-1,3 galactosyltransferase gene, preparation of DNA construct containing interrupted mouse α-1,3 galactosyltransferase gene (pNeoαGT10.8B), production of α-1,3 galactosyltransferase homologous knockout mice by injecting mouse ES cells transfected by pNeoαGT10.8B into blastocyst and confirm the lack of the galactose α-1,3 galactose epitope in said knockout mice by anti-gal and IB4 lectin binding assay, and the resistance of spleen cells from knockout mice to lysis by human serum.

The specification of the present application does not disclose any porcine ES, or PGC cells which can be used for the production of transgenic pigs. There is no working example of how to make and use α-1,3 galactosyltransferase homologous knockout pigs by microinjecting DNA into porcine fertilized eggs, embryo, or by transfecting porcine ES or PGC cell with DNA construct and injecting said cells into porcine blastocyst, porcine morula, co-culturing said ES

cell with a zona pellucida-disrupted porcine morula, or fusing porcine cell with an enucleated porcine oocyte. Houdebine, 1994 (U) points out that ES cells can be used to generate transgenic animals, but this approach remains restricted to mice, ES cells from other species are not presently available. Seamark, 1994 (V) points out that even pig's pluripotent ES cells can be created, no group has demonstrated totipotency of these cells through reinstating their genome within a germ line, and procedures for reinstating the ES cell genome into a germ line are still far from routine. Furthermore, even if the claimed pigs could be made, phenotype is not disclosed, so one would not know how to use them. Small changes in the environment the embryo is exposed to can impact on development with long-term implications on health and welfare. For example, in the mouse, brief exposure of preimplantation embryos to in vivo culture conditions can both result in substantial phenotypic variation and predicate the subsequent expression and penetration of some transgenes. Asynchrony between the stage of development of the embryo and tract at embryo transfer can also affect development. Therefore, it is not feasible and unpredictable at the time of the present application to make and use a transgenic porcine ES , PGC, or egg's cell comprising at least one inactivated α-1,3 galactosyltransferase gene, or a transgenic pig homologous for an inactivated α-1,3 galactosyltransferase gene, or the cells, cell lines derived from said transgenic pig.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the claimed inventions. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation

necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2, 46-51 and 63-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gustafsson et al., 1994 (W) in view of Seamark, 1994 (V) and Sandrin et al., 1995 (X).

Claims 1, 2, 46-51 and 63-67 are drawn to nucleic acid molecule comprising SEQ ID No.7, SEQ ID No.7 within the scope of the degeneracy of the genetic code, sequences hybridize to SEQ ID No.7 under standard high stringency condition, a host cell transformed by said nucleic acid molecule, DNA construct comprising a disrupted porcine α-1,3 galactosyltransferase gene, a method of generating a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase gene by introducing a DNA construct comprising said inactivated gene into porcine cells; cells and cell lines derived from transgenic pig homozygous for an inactivated α-1,3 galactosyltransferase gene.

Gustafsson et al. teaches the cloning of cDNA coding for pig α-1,3 galactosyltransferase gene, inhibiting the expression of Gal α-1,3 Gal epitope on pig endothelial cells in culture, introduction of ribozyme constructs designed to inhibit the expression of the pig α-1,3 galactosyltransferase gene *ex vivo* into pig organ employing adenoviral- or liposome-vector system, and suggest the use of pig tissues in xenotransplantation between pig and human. Gustafsson et al. does not reveal the cDNA sequence of pig α-1,3 galactosyltransferase, or teach the use of recombinase in preparing DNA construct of making cells containing an inactivated α-1,3 galactosyltransferase gene. Sandrin et al. reveals the cDNA sequence (GenBank Accession No. L36535) of a pig α-1,3 galactosyltransferase gene. Seamark teaches homologous recombination, use of FLP recombinase target sites within the genome to allow both insertion and exchange of transgene cassettes through the FLP recombinase system. Thus, it would have been obvious for a person of ordinary skill at the time of invention to have isolated and purified said nucleic acid molecule set forth above, a host cell transformed with said nucleic acid molecule, or have made a DNA construct compsising a disrupted α-1,3 galactosyltransferase, a porcine cell or cell line comprising at least one inactivated α-1,3 galactosyltransferase. Therefore, claims 1, 2, 46-51 and 63-67 are rejected under 35 U.S.C 103(a).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton can be reached on (703) 308-2801. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800